

REMARKS

Claims 1-40 are pending. Claims 1, 27, 29, 32 and 35 are amended. The amendments add no new matter.

Rejection under 35 U.S.C. §102(e) over Enzelberger et al.:

Claims 1-40 are rejected as lacking novelty under 35 U.S.C. §102(e) in view of the new reference, Enzelberger et al., U.S. 6,960,437. The Office Action states the following with regard to the new reference:

Enzelberger et al. teach a polymerase chain reaction (PCT) apparatus of claim 1, comprising (i) a solution holder separately hold plurality of samples of reaction mixture (see at least col. 2, line 40-44, col. 16, line 39-45, col. 51, line 14-18) (ii) a heat exchanging structure to cyclically control specified duration and temperature of plurality of samples (see at least col. 2, line 40-64, col. 26, line 30-67, col. 27, line 1-67, col. 28, line 1-67, col. 29, line 1-67, col. 30, line 1-67, col. 51, line 14-18) dispensing mechanism to dispense, aliquots from each sample of the plurality of samples at respective different cycles of an amplification regiment (see at least col. 2, line 44-56, col. 16, line 30-67, col. 17, line 1-7, col. 18, line 1-28, col. 51, line 19-26 indicating control channel as dispensing mechanism for withdrawal of portions of samples at different temperature cycles).

The Office Action concludes on this basis that claims 1-40 are anticipated by the '437 reference. Applicants respectfully disagree.

Applicant submits that the '437 reference does not teach an aliquot dispensing mechanism to dispense, from each sample of a set of plural samples held by the solution holder, plural aliquots of a given sample at respective different cycles of an amplification regimen, to separate aliquot holders as required by each of the instant claims. The Office Action points to the following sections of the '437 disclosure in support of the conclusion that the '437 reference teaches such a mechanism:

Devices of this type can also include a plurality of control channels, each formed within an elastomeric material and separated from one of the reaction chambers by an elastomeric membrane, the membrane being deflectable into one of the reaction chambers in response to an actuation force applied to the control channel. As a result of such actuation, sample can be transported between the reaction chambers. In some instances, the plurality of reaction chambers are in fluid communication such that substantially all of the sample within the plurality of

reaction chambers is collected at one of the plurality of reaction chambers upon actuation of the control channels associated with the other reaction chambers.

Column 16, lines 30-67 and Column 17, lines 1-7:

An example of another configuration that can be utilized in thermocycling reactions is illustrated in FIG. 2. As with the microfluidic device illustrated in FIG. 1, this device 200 also is composed of two layers that are joined together: a first layer into which flow channels are formed and through which sample and reactants flow, and a second layer into which control channels are formed. After these two layers are joined such that the control channels properly intersect with the appropriate flow channels, the resulting device is typically affixed to a support (e.g., glass). Consistent with the architecture of the device shown in FIG. 1, the layer with the flow channels has a plurality of sample inputs 202a and 202b, a mixing T-junction 204, and an output channel 206 (see FIG. 2). This device, however, differs in that a plurality of reaction chambers 208a, 208b and 208c are disposed along the primary flow channel 210. In general, a different reaction chamber is provided for each different temperature region that is needed to conduct the analysis of interest.

The plurality of reaction chambers 208a, 208b and 208c are in fluid communication with other reaction chambers in the system. The reaction chambers 208a, 208b, and 208c are also operatively disposed with respect to a control channel 212a, 212b and 212c, respectively. Actuation of the control channel associated with a reaction chamber causes the solution within the chamber to be expelled. As depicted in FIGS. 3A and 3B, because the control channel 304 and reaction chamber 308 are formed within an elastomeric material 302 (that is attached to a substrate 310) and separated by a flexible elastomeric membrane 312, actuation of the control channel 304 results in deflection of the membrane 312 into the reaction chamber 306. Because the membrane 312 can mold to the shape of the reaction chamber 306, essentially all solution and reactants 308 within the reaction chamber 306 is forced out of the actuated reaction chamber and into an unactuated reaction chamber. Reaction chambers 306 whose associated control channel 304 is actuated are sometimes referred to simply as actuated chambers; conversely, reaction chambers 306 whose control channels 304 are not actuated are referred to as unactuated reaction chambers. The reaction chambers in certain devices are fluidly connected such that actuation of all the control channels but one results in substantially all of the solution in the actuated reaction chambers being forced into the one reaction chamber whose control channel is not actuated (i.e., the sole unactuated reaction chamber).

Column 18, lines 1-28:

Thus, referring once again to FIG. 2, once sample and reagents have had sufficient exposure to the temperature of reaction chamber 208a, substantially all of the solution in each of the reaction chambers and other sections of the flow channel system can be forced into reaction chamber 208b by actuating control channels 212a and 212c associated with reaction chambers 208a and 208c, respectively. Similarly, solution can be forced into reaction chamber 208c by actuating control channels 212a and 212b associated with reaction chambers 208a and 208b.

For nucleic acid amplifications, the general considerations set forth above with respect to the device shown in FIG. 1 apply to methods performed with device 200 as well. The temperature of each reaction chamber is set for the temperature that promotes the annealing, extension and denaturation processes. Solution is transported between the different reaction chambers by selectively actuating the appropriate control channels as just described. Any amplified product formed and unreacted reagents can be transported out of the reaction chambers via the outlet.

Detection of unreacted reagents and/or product can be conducted at one or more than one of the reaction chambers. Alternatively, detection can be conducted after reagents and product have been transported from the reaction chambers and at another location on the device. As with the other device, another option is to remove a portion of the withdrawn solution and to analyze the withdrawn solution on another system.

Column 51, lines 19-26:

The microfluidic device of claim 8, further comprising a plurality of control channels, each formed within an elastomeric material and separated from one of the reaction chambers by an elastomeric membrane, the membrane being deflectable into one of the reaction chambers in response to an actuation force applied to the control channel; and wherein the sample can be transported between the reaction chambers by actuation of the control channels.

These passages are cited as teaching a “control channel as dispensing mechanism for withdrawal of portions of samples at different temperature cycles.” This is incorrect. First, as described in the ‘437 reference at column 2, lines 44-56, the “control channel” permits the transport, upon “actuation,” of sample *between* reaction chambers: see lines 50-51, which recite “As a result of such actuation, sample can be transported between the reaction chambers.” This

is not “dispensing plural aliquots of a given sample at respective different cycles of an amplification regimen, to respective separate aliquot holders” as required by each of the independent claims. Specifically, transporting a reaction mixture from one reaction chamber to another is not “dispensing plural aliquots” of the reaction mixture. Transporting the whole reaction mixture from one chamber to another is not dispensing an “aliquot,” i.e., the whole reaction mixture cannot be an aliquot. The ‘437 reference expressly teaches the transport of the entire sample volume from chamber to chamber in text cited in the Office Action:

Actuation of the control channel associated with a reaction chamber causes the solution within the chamber to be expelled. As depicted in FIGS. 3A and 3B, because the control channel 304 and reaction chamber 308 are formed within an elastomeric material 302 (that is attached to a substrate 310) and separated by a flexible elastomeric membrane 312, actuation of the control channel 304 results in deflection of the membrane 312 into the reaction chamber 306. *Because the membrane 312 can mold to the shape of the reaction chamber 306, essentially all solution and reactants 308 within the reaction chamber 306 is forced out of the actuated reaction chamber and into an unactuated reaction chamber.* Reaction chambers 306 whose associated control channel 304 is actuated are sometimes referred to simply as actuated chambers; conversely, reaction chambers 306 whose control channels 304 are not actuated are referred to as unactuated reaction chambers. The reaction chambers in certain devices are fluidly connected such that actuation of all the control channels but one results in substantially all of the solution in the actuated reaction chambers being forced into the one reaction chamber whose control channel is not actuated (i.e., the sole unactuated reaction chamber). (‘437 reference, column 16, line 52, to column 17, line 7; emphasis added)

That an aliquot cannot be the whole reaction mixture is supported by definitions in the specification, language within the claims themselves, and by the dictionary definitions of the term “aliquot.”

First, the specification defines an “aliquot” as referring “to a sample volume taken from a prepared sample or from a reaction mixture” (page 9, lines 9-10). The specification also expressly defines “dispensing an aliquot from the reaction mixture at plural stages” as follows:

“As used herein, the phrase ‘dispensing an aliquot from the reaction mixture at plural stages’ refers to the withdrawal or extrusion of an aliquot at least twice, and preferably at least 3, 4, 5, 10, 15, 20, 30 or more times during an amplification regimen. A ‘stage’ will refer to a point after a given number of cycles, or, where the amplification regimen is non-cyclic, will refer to a selected

time after the initiation of the regimen.”

As expressly defined in the specification, then, “dispensing plural aliquots” requires withdrawal or extrusion of an aliquot “at least twice, and preferably at least 3, 4, 5, 10, 15, 20, 30 or more times during an amplification regimen.” Applicant submits that moving the whole reaction mixture from one chamber to another, even if done so repeatedly, cannot be interpreted as “dispensing plural aliquots” because once the whole mixture is transferred to another chamber, there is nothing left of the mixture from which to take another aliquot. The language “dispense.... plural aliquots” in the claims themselves is therefore not amenable to any interpretation that a mechanism that effects movement of the whole reaction mixture to another reaction chamber is “an aliquot dispensing mechanism to dispense plural aliquots of a given sample at respective different cycles of an amplification regimen” as recited in the claims.

In further support of the fact that an aliquot is not an entire reaction mixture, the American Heritage Dictionary definition of “aliquot” is:

adj. Of , relating to, or denoting an exact divisor or factor of a quantity, especially of an integer.
n. An aliquot part.

("aliquot." *The American Heritage® Dictionary of the English Language, Fourth Edition*. Houghton Mifflin Company, 2004. 21 Sep. 2007. <Dictionary.com <http://dictionary.reference.com/browse/aliquot>>.)

Thus, the use of the term “aliquot” as a noun, as it is used in the claims, refers to a part of the whole. The American Heritage Stedman’s Medical Dictionary defines the term as:

n. “A portion of the whole, especially one of two or more samples of something that have the same volume or weight.”

"aliquot." *The American Heritage® Stedman's Medical Dictionary*. Houghton Mifflin Company. 21 Sep. 2007. <Dictionary.com <http://dictionary.reference.com/browse/aliquot>>.

This definition, which is clearly on point for the way the term is used in the specification and claims, again requires that an “aliquot” is a “portion of the whole” – i.e., an aliquot of a reaction mixture it is not the whole reaction mixture volume. The ‘437 reference therefore does not teach “an aliquot dispensing mechanism to dispense.... plural aliquots of a given sample at respective different cycles of an amplification regimen, to respective separate aliquot holders.”

Not only does the '437 reference not teach “an aliquot dispensing mechanism to dispense, from each sample of a set of the plural samples held by the solution holder, plural aliquots of a given sample at respective different cycles of an amplification regimen,” the reference does not teach any mechanism that dispenses plural aliquots “to respective *separate aliquot holders*” as also required by each of the subject claims. Just as transport of a whole sample to another reaction chamber is not dispensing an aliquot, transport of a whole sample to another reaction chamber is not dispensing “to respective separate aliquot holders.” Further, from the plain meaning of the term “respective separate aliquot holders,” *each* of the plural aliquots of a given sample taken at respective different cycles of an amplification regimen must be dispensed into a *separate* aliquot holder. Thus, plural aliquots can be taken from a single reaction mixture at different cycles of an amplification regimen – their dispensing or placement into separate aliquot holders permits the collection of a set of separate aliquots from each of a plurality of reaction mixtures over the course of the amplification regimen for analysis. No such separate aliquot holder or device is described in the '437 reference.

In view of the above, the '437 reference does not teach “an aliquot dispensing mechanism to dispense, from each sample of a set of the plural samples held by the solution holder, plural aliquots of a given sample at respective different cycles of an amplification regimen, to respective separate aliquot holders” as required by independent claims 1, 29, 32 and 35, or “an automatic dispensing mechanism to automatically dispense, from each sample of a set of the plural samples held by the solution holder, plural aliquots of a given sample at respective different cycles of an amplification regimen to respective separate aliquot holders” as required by independent claim 27. Because it fails to teach all elements of the invention of claims 1, 27, 29, 32 or 35, the '437 reference cannot anticipate the invention as claimed in these independent claims. Because the '437 reference does not teach all elements of independent claims 1, 27, 29, 32 or 35, the '437 reference cannot anticipate the invention as claimed in claims that depend from them. Withdrawal of the novelty rejections of claims 1-40 over the '437 reference is respectfully requested.

In view of the above, Applicant submits that all issues raised in the Office Action have been addressed herein. Reconsideration of the claims is respectfully requested.

Respectfully submitted:

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